Pathology of the eye and its surrounding structures is unique due to the many tissue types, close proximity of essential structures, altered manifestations of disease processes in the ocular environment, and ability to identify key anatomic structures relevant to ocular function in pathologic specimens. The ophthalmic pathologist complements the observations of ophthalmologists who routinely perform biomicroscopy of the eye with the ability to detect small collections of cells – essentially gross pathology of the live human eye. In this way the eye pathologist plays a unique role in discerning and communicating true clinicopathologic diagnoses and can comment upon future clinical options for the patient that will affect survival, ocular function, comfort, and cosmesis. Eye pathology is at once arcane and cutting edge in its methods and interpretations.

Many Tissues, Functions, and Presentations in a Very Small Space

The eye is unique in that a number of discrete tissues are all packed within its confines, each affected by lesions peculiar to the tissue type and often highly localized within the tissue. Thus, grossing eye specimens is an art which requires intimate knowledge of eye anatomy and pathology, and the skill to divide specimens in order to optimize information that may be deduced from microscopic sections. Frequently, this requires working closely with technicians to produce sections that inform the pathologic status of anterior ocular structures (e.g., cornea, iris, and lens), posterior structures (e.g., retina, choroid, sclera, and optic nerve), and important lesions such as wounds or tumors, all in a microscopic section. In so doing, the pathology of each tissue and the relationship of the alterations are best understood.

Eye in Systemic Disease

Each of the tissues comprising the eye is affected by different diseases and each tissue may be affected by the same disease process in different ways. Moreover, diseases which also affect other organs commonly show different patterns when they involve eye tissues. A good example is primary ocular lymphoma, whose systemic involvement is usually limited to the central nervous system. This lymphoma causes malignant retinal and vitreous infiltrates, but has a selective distribution, inducing only benign choroidal inflammatory infiltrates in the same specimens. Systemic diseases may cause ocular deposits with characteristic distributions. Examples include corneal cysteine crystals of cystinosis, protein-containing ciliary body cysts of multiple myeloma, or diffuse choroidal cellular infiltrations of metastatic melanoma or carcinoma which are often accompanied by characteristic exudative retinal detachments. The immune privileged intraocular environment also affects the presentation of systemic rheumatologic diseases, allograft rejection, and inflammatory responses to infectious agents and foreign objects, while providing the basis of inflammations unique to the eye, such as phacoanaphylaxis and sympathetic ophthalmia. The ocular environment causes these and other inflammatory diseases to exhibit unique clinical and pathologic features that, when recognized in conjunction with one another, may provide a diagnosis, even when the minute amount of tissue present on the histopathologic slides would otherwise be insufficient to arrive at one.

The ophthalmic pathologist also renders diagnoses on a variety of entities peculiar to the eye, some of which have important systemic implications. The eye demonstrates distinctive lesions of phakomatoses, a group of familial diseases that produce a constellation of lesions affecting different organ systems. In these diseases, the ophthalmic diagnosis and its pathologic confirmation frequently reveals the presence of the disease whose other, often life-threatening manifestations, may be sought in the patient and relatives. These diseases include neurofibromatosis, tuberous sclerosis, and von Hippel-Lindau disease. Other lesions, largely restricted to the eye, may be associated with lethal systemic diseases. These include sebaceous carcinoma and adenoma with gastrointestinal malignancy, Gardner's syndrome with systemic neoplasia, retinoblastoma with osteosarcoma and other malignancies, uveal melanocytic proliferations with visceral malignancies, thickened corneal nerves with multiple endocrine neoplasia, and ocular melanocytosis with melanoma. When these lesions are recognized by an
ophthalmic pathologist who is well aware of the possible associated systemic malignancies, lives can be saved.

**Small Specimens Magnify Need for Caution**

In diagnosing entities involving the ocular structures, ophthalmologists often can provide only small biopsy specimens without severe adverse consequences to the eye. These specimens, much more minute than that commonly processed in the pathology laboratory, require special handling to avoid specimen loss and maximize the information that can be gleaned from the relatively meager amount of material available. Moreover, the diagnosis many times rests on careful examination of individual cells within a sample. Thus, a knowledge of the clinical setting, ophthalmic diseases, site of involvement, and method of biopsy all play a role in arriving at the diagnosis. The ophthalmic pathologist commonly suggests further studies and/or treatment based on these specimens while understanding that the structures involved and adjacent delicate tissues may require preservation by alternative treatments and narrow surgical margins. This is particularly germane to the eyelids, conjunctiva, and other structures surrounding the eye where resections are limited by the proximity of structures vital to the eye and adjacent structures, including the brain. In such cases, careful and complete assessment of closely cropped surgical margins is mandatory to determine the prognosis and adjunctive treatment.

**(Ophthalmic Pathology in Medical Advances)**

Ophthalmic pathology has been at the forefront of a number of medical technological advances. For example, the first oncogene discovered was that associated with retinoblastoma whose association with osteosarcoma was initially recognized in 1964. Some of the first extensive genetic classifications of disease and identification of specific genetic defects in medicine were first performed in conjunction with ophthalmic pathology. Among these have been myriad corneal dystrophies, some distinguished by distinctive histologic tissue stains, many of which have been shown to be different mutations of a few genes. Another example has been the classification of a variety of retinal dystrophies whose genetic etiology was recognized at the outset of medical genetics and whose extensive genetic classification continues to be at the cutting edge of genetic studies.

Ocular pathology was the first to document in detail the tissue effects of medical lasers which were introduced into medical practice by ophthalmologists after their invention in 1960. Ophthalmic pathology has also studied the effects of prosthetic devices, most notably plastic intraocular lenses, stents, and scleral supportive prostheses for retinal attachment. This trend continues as reflected in an increased understanding of tissue responses to laser treatment including the Intralase, a laser invented at the University of Michigan and now widely used worldwide for LASIK refractive surgery.

Primary intraocular lymphoma in an elderly woman. Fundus photograph of tumor (yellow-white) infiltrates of retina (left) and immunohistochemical stain of malignant lymphoma (right). This patient had an undetected region of lymphoma in the brain, which was noticed by an ophthalmologist and cured by treatment.
Cytomegaloviral retinitis in a young man. Fundus photograph of viral-induced retinal necrosis and white infiltrates (left) and retinal biopsy showing necrosis and immunohistochemically-stained viral particles in retinal cells (right). The patient was diagnosed as having immunosuppression and was successfully treated with antiviral agents.

Sebaceous carcinoma in an elderly woman. Photograph of left eye initially diagnosed as having severe blepharoconjunctivitis which proved to be unresponsive to antibiotic treatment and biopsy demonstrating malignant cells containing foamy cytoplasm diagnostic of sebaceous carcinoma (right). Genetic testing following exenteration revealed a mutation of the MSH2 gene. Systemic evaluation revealed a gastrointestinal malignancy that was successfully treated.

Retinoblastoma in a young girl. Photograph of left eye containing retinoblastoma and photomicrograph of tumor after enucleation demonstrating classic Flexner-Wintersteiner rosettes (right). This patient was also found to have tumor in the right eye, which was treated and saved. Subsequent identification of a mutation of the RB1 gene means that she will require monitoring for other systemic malignancies to which she is predisposed.
Heritable corneal dystrophies. Lattice corneal dystrophy with Congo red-positive deposits (left) and granular corneal dystrophy with trichrome-positive deposits (right). These clinically and pathologically distinctive dystrophies are due to different mutations of the βig-h3 gene. Vision can be restored by corneal transplantation but the dystrophies may recur in the grafts.

**TABLE I: EXAMPLES OF ENTITIES UNDER THE PURVIEW OF THE OPHTHALMIC PATHOLOGIST**

**Eye and surrounding structures:**
- Melanoma*
- Metastatic carcinoma*
- Sarcoidosis*
- Phacomatoses*

**Intraocular:**
- Melanoma*
- Primary ocular lymphoma*
- Cytomegaloviral retinitis*
- Herpetic retinitis*

**Cornea:**
Numerous infections including protozoal, viral, and fungal
Numerous dystrophies affecting epithelium, stroma, and endothelium*
- Allograft rejection
- Surgical complications

**Conjunctiva:**
- Primary acquired melanosis/melanoma
- Malignant melanoma arising in nevus
- Carcinoma *in situ*, including HPV-induced and sporadic
- Numerous infections and inflammations

**Eyelid and eyelid margin:**
- Sebaceous carcinoma*
- Malignant melanoma
- Inflammatory diseases

**Orbit:**
- Lacrimal gland neoplasms
- Orbital inflammatory pseudotumor*

* Diseases with possible associated systemic manifestations
Introduction: Ophthalmic Pathology & American Association of Ophthalmic Pathologists (AAOP)

Victor M. Elner, MD, PhD
University of Michigan

USCAP
March 2007
San Diego, CA
Singular Characteristics of Eye Pathology

- Many tissue types
- Proximity of essential structures
- Altered manifestations of disease in the eye
- Clinicopathologic diagnoses that affect survival, eye function, comfort, and cosmesis
Many Tissues, Functions, and Presentations in a Very Small Space

- Many discrete tissues packed into confines of the eye
- Each tissue affected by lesions peculiar to the tissue type
- Grossing is essential to analysis as disease may be highly localized
Eye in Systemic Disease

- Each tissue in the eye affected by different diseases
- Each tissue may be affected in different ways by the same disease process
- Systemic diseases may exhibit different patterns in eye tissues
Primary Intraocular Lymphoma

Primary ocular lymphoma in an elderly woman. Fundus photograph of yellow-white tumor infiltrates in retina and mottling of choroid.

CD20+ large cell lymphoma in retina. Choroid contained reactive lymphocytic infiltrate.

Undetected lymphoma in brain was diagnosed and successfully treated after ocular diagnosis.
Cytomegaloviral Retinitis

Cytomegaloviral retinitis in a young man. Fundus photograph of viral-induced retinal necrosis.

Typical CMV-induced retinal necrosis. Intranuclear inclusions showing immunopositivity for CMV antigen.

The patient was found to be immunosuppressed and was successfully treated with anti-viral agents after ocular diagnosis.
Entities Peculiar to the Eye

- Some have important systemic implications, for example:
  - Phakomatoses
  - Sebaceous carcinoma and adenoma
  - Gardner’s syndrome
  - Retinoblastoma
  - Uveal melanocytic proliferations

- Some appear restricted to the eye, for example:
  - Corneal dystrophies
  - Lens abnormalities
  - Developmental or acquired lesions
Sebaceous Carcinoma

Sebaceous carcinoma in an elderly woman. Initial diagnosis of blepharoconjunctivitis unresponsive to antibiotic treatment.

Biopsy demonstrating malignant epithelial cells with abundant foamy cytoplasm diagnostic of sebaceous carcinoma

Genetic testing after exenteration showed MSH2 gene mutation. A gastrointestinal malignancy was found and successfully treated.
Retinoblastoma

Retinoblastoma in a young girl. Photograph of left eye containing white-cream colored tumor.

Photomicrograph of tumor demonstrating classic Flexner-Wintersteiner rosettes and necrosis.

Retinoblastoma later discovered in other eye, which was treated and saved. Detection of RB1 gene revealed predisposition for systemic malignancies.
Entities Peculiar to the Eye

- Some have important systemic implications, for example:
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  - Sebaceous carcinoma and adenoma
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  - Uveal melanocytic proliferations

- Some appear restricted to the eye, for example:
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  - Lens abnormalities
  - Developmental or acquired lesions
Lattice corneal dystrophy with Congo red-positive deposits.

Granular corneal dystrophy with trichrome-positive deposits.

The dystrophies are clinically and pathologically distinctive; both are due to \( \beta \text{ig-h3} \) gene mutations. Allografts for vision restoration may suffer recurrence.
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* Diseases with possible associated systemic manifestations
Small biopsy specimens often obtained to avoid adverse consequences to the eye.

Specimens require special handling of meager material.

Clinical setting, differential diagnosis, exact site, and biopsy method all key.

Closely-cropped surgical margins require careful and complete assessment.

Alternative treatments may be suggested to preserve vision while adequately treating disease.
Ophthalmic Pathology in Medical Advances

- Eye pathology at the forefront of medical technological advances, for example:
  - Oncogenes and retinoblastoma
  - Classifications of genetic diseases
  - Laser effects on tissues
  - Prosthetic devices such as lenses, stents, and supportive prostheses
  - LASIK
American Association of Ophthalmic Pathology (AAOP)

- Originates from members of various ophthalmic pathology societies
- First national society with open membership to all qualified individuals
- Annual joint meeting with the American Academy of Ophthalmology:
  - Day-long pre-meeting
  - One-half day meeting open to Academy members
- International component